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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/720,192	LAQUEYRERIE ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) *20,21,23,24 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/25/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Amendment submitted on 1/26/05 is made. Claims 19-21 and 23-30 are currently pending. Claims 20, 21, 23, 24, and 27-30 were previously withdrawn from further since they are drawn to a non-elected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 19, 25 and 26 are currently under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 19, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is vague and indefinite because it is unclear what is encompassed by "a portion of" the amino acid sequence of SEQ ID NO:2 or 3". "A portion of" reads on as few as one or two amino acids. However, this does not appear to be Applicant's intention. There is no size requirement or functional requirement which allows for the 'portion' to read on a single amino acid. The metes and bounds of the invention cannot be understood because the

specification and claims fail to define what is encompassed by "a portion of". The term "portion" in claim 19 is a relative term which renders the claim indefinite. The term "portion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is requested.

Additionally, the article "a" should be inserted before the word 'polypeptide' in line 4 of claim 19.

Response to Applicants' Argument regarding 'a portion of':

Applicants argue that a skilled artisan knew from general technical knowledge, the sizes of protein fragments that are required for inducing an immune response. This has been carefully considered, but is not deemed persuasive. The instant claim does not require the immune response to be generated by the protein which is 'a portion of SEQ ID NO:2 or 3" rather it is possible that the immune response is solely being generated by the polypeptide comprising the antigenic determinant. The claim still reads on one or two amino acids linked to an antigenic polypeptide. As stated above, the term "portion" in claim 19 is a relative term which renders the claim indefinite. The term "portion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not define the sizes of acceptable portions, nor does it state that the portion has to be of a certain length or generate an immune response against *Mycobacterium.*

The prior art references cited are irrelevant regarding this matter as they are drawn to immunogenic epitopes. The claim, nor the specification teaches that the portion is to be an immunogenic epitope. No function or size is recited in the specification.

Claim Rejections - 35 USC § 112-New Matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 19, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 recites 'a protein having *conservative substitution* in the amino acid of SEQ ID NO:2 or 3....". The instant specification fails to teach conservative substitutions. There is no written support for this language. Applicants have pointed to page 5, lines 13-17, of the specification which states that the "present invention also includes proteins having secondary differences or limited variations in their amino acid sequences which do not functionally modify them". This passage does not provide adequate support for "conservative substitution". Secondary differences and limited variations which do not modify the proteins functionally do not necessarily have to be 'conservative substitutions'. Non-conservative substitutions, deletions, additions which do not

functionally modify the protein, such as in a position not critical to function, are also secondary differences or limited variations in their amino acid sequences which do not functionally modify the proteins. The specification fails to teach or recite conservative substitutions. This subject matter must be removed from the claim.

Double Patenting

NOTE: APPLICANTS FAILED TO ADDRESS THIS REJECTION IN THEIR RESPONSE OF 1/26/05:

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 19, 25 and 26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,676,945. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims recite the use of "at least a portion" of SEQ ID Nos: 2 or 3 in a hybrid protein linked to a polypeptide comprising an antigenic determinant, whereas the patented claims

recite the use of one of the full-length proteins of SEQ ID NO:2 or 3 in the hybrids linked to an antigenic polypeptide. The scope of the instant claims and the patented claims would be obvious, each over the other, as "at least a portion" includes the full-length sequences. Additionally, a polypeptide comprising an antigenic determinant and an antigenic polypeptide are the same.

NOTE: The elected claims were presented in parent case, now US Patent No. 6,676,945. These claims were amended during the prosecution of the parent case in order to overcome the 112, 1st and 2nd paragraph and prior art rejections which is why they are now different from the pending claims. It is brought to Applicants intention that if the claims are amended in a similar manner the following ***Statutory*** Double Patenting Rejection will be made:

Claims 19, 25 and 26 are rejected under the judicially created doctrine of double patenting over claims 1-12 of U. S. Patent No. 6,676,945 since **the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.**

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: hybrid proteins comprising SEQ ID Nos: 2 or 3 and an antigenic polypeptide.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 19, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a hybrid protein comprising a polypeptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3 linked to an antigenic polypeptide which is able to induce an immune response in an animal" and methods of inducing an immune response in an animal through the administration of said hybrid protein, does not reasonably provide enablement for "a hybrid protein comprising at least a portion of the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3, or a protein having conservative substitutions in the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3 and a polypeptide comprising an antigenic determinant which is able to induce an immune response in an animal" or for a method of methods of inducing an immune response in an animal through the administration of said hybrid protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to hybrid proteins and pharmaceutical compositions comprising said hybrid proteins which comprise "at least a portion" of the protein of SEQ ID Nos.: 2 or 3; and proteins having conservative substitution in the amino acid sequence of SEQ ID NO:2 or 3. However, the specification provides no guidance as to what these substitutions may be, nor does it define what is encompassed by 'a portion of'. As stated in the New Matter rejection above, the specification fails to even mention conservative substitutions, much less provide examples. No guidance as to what amino acids may be changed without

causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be substituted. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. Selective could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein on the *Mycobacteria*, and be ineffective in treating or inducing an immune response against disease caused by *Mycobacteria*.

Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different

amino acid substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Given the lack of guidance contained in the specification regarding acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's Arguments:

Applicants argue that it would only take routine experimentation to make peptide fragments of SEQ ID Nos: 2 and 3. They argue that "various amino acid residues and their physical chemical properties were sufficiently well characterized, at the date of the invention, for having been classified so that the one skilled in the art knows well which amino acid substitution might be effected". These arguments have been fully and carefully considered but are not deemed

persuasive. As stated above, the phrase 'conservative substitution' is new matter. The specification has failed to teach a specific size or function for the 'portion of' SEQ ID NO:2 or 3. The specification has also failed to teach acceptable substitutions which can be made to the proteins of SEQ ID NO:2 or 3 without modifying them functionally. With regard to the characterization of individual amino acids, every protein is different. Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Given the lack of guidance contained in the specification regarding acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 19, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wieles et al (Infect. Immun. Jan. 1994. 62(1): 252-258) in view of Marchal et al (WO 92/21758) Note: US 6,060,259 was used for English translation of the WO patent.

Wieles et al disclose a protein antigen from *M.leprae* which is related to the secreted *M.tuberculosis* protein MPT32(abstract). The protein disclosed by Wieles et al has "at least a portion of the sequence SEQ ID NO. 2 and 3". Figure 17 and page 8, lines 20-23, of Applicant's specification teach the homology of Wieles= protein to the proteins disclosed in SEQ ID Nos: 2 and 3. Sequence analysis revealed that the protein of Wieles has an overall similarity of 60% and a best local similarity of 68.6% to Applicants' SEQ ID NO: 2 and 3. Immunological assays comprising the protein and a detection agent were performed (p. 254 and p. 256).

However, Wieles et al do not teach the use of their protein antigens in a hybrid protein.

Marchal et al disclose proteins from *Mycobacterium bovis* which have a molecular weight of approximately 44.5 to 47.5 kD. Said proteins have molecular weights of about 45 kD or about 47 kD and isoelectric pH values of about 3.7 (45 and 47 kD proteins) and 3.9 (47 kD proteins). Proteins or hybrid proteins comprising a part of their sequences may be used as vaccines or medicaments, or for the detection and monitoring of tuberculosis, in particular in humans and in

cattle. The reference teaches that hybrid proteins comprising the whole or part of the 45-47kDa *Mycobacterium* proteins and a sequence corresponding to an antigenic determinant. It is taught that the antigenic determinant can be a fragment of a protein or glycoprotein antigen, in order to obtain immunogenic compositions able to induce the synthesis of antibodies directed against these multiple antigenic determinants. It is taught that the antigenic determinants or fragments may be, for example, diphtheria toxin or fragments thereof, tetanus toxin, the surface antigen of hepatitis B virus, poliomyelitis virus VP1 antigen, etc. These hybrid proteins allow for a dual immune response which includes immunization to antigenic determinants not present on the *Mycobacterium* proteins. See column 4, lines 13-35.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that all or part of the *Mycobacterium* proteins disclosed by Wieles et al could be used to form a hybrid protein comprising a antigenic polypeptide which can induce antibodies in a host because Marchal et al teach similar and related *Mycobacterial* proteins to those disclosed by Wieles et al and teaches that these proteins linked to antigenic protein or fragment of a protein or glycoprotein antigen, can be used to obtain immunogenic compositions able to induce the synthesis of antibodies directed against these multiple antigenic determinants. Marchal teaches that the antigenic determinants or fragments may be, for example, diphtheria toxin or fragments thereof, tetanus toxin, the surface antigen of hepatitis B virus, poliomyelitis virus VP1 antigen, etc. One of ordinary skill in the art would have been motivated to make hybrid

proteins using the proteins taught by Wieles and an antigenic polypeptide such as those taught by Marchal et al. because the proteins of Marchal are homologous to those taught by Wieles and one of ordinary skill in the art would have a reasonable expectation of achieving a strong dual immune response in a host through the administration of said hybrid proteins.

Response to Applicants' Arguments:

Applicants argue that Wieles' protein is only 47% homologous to the claimed proteins. They also argue that Weiles does not suggest any technical mean which would enable or even motivate, one of ordinary sill to isolate and characterize the proteins of SEQ ID NO:2 or 3. They also argue that the protein of Wieles is from a different species of *Mycobacterium* and therefore would not raise a protective immune response against tuberculosis. These arguments are not commensurate in scope with the claimed invention. The claims do not require the isolation of SEQ ID NO:2 or 3, they only require 'a portion of" SEQ ID NO:2 or 3 which is as small as a few amino acids. The 'portion' could be from a completely different protein as long as it contained a 'portion'. The claims and methods do not require raise a protective immune response against tuberculosis. Claim 19 is merely drawn to a hybrid protein. Further, even if an intended use was inserted in claim 19, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. With regard to claims 25 and 26, the methods only require 'inducing an

immune response'. They do not require the immune response to be protective against *M.tuberculosis*. much less against *Mycobacterium.*

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 4/6/05

Jennifer Graser
Primary Examiner
Art Unit 1645